

Preclinical Investigations of GlyT-1 Inhibition as a new Concept for Treatment of Alcohol Dependence

AKADEMISK AVHANDLING

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Avhandlingen baseras på följande arbeten:

- I. Molander A, **Höifödt H**, Löf E, Ericson M, Söderpalm (2007) The Glycine Reuptake Inhibitor Org25935 Decreases Ethanol Intake and Preference in Male Wistar rats. *Alcohol and Alcoholism*, 42:11-18
- II. **Höifödt Lidö H**, Stomberg R, Fagerberg A, Ericson M, Söderpalm B (2009) The Glycine Reuptake Inhibitor Org25935 Interacts with Basal and Ethanol-induced Dopamine Release in Rat Nucleus Accumbens. *Alcohol Clin Exp Res* 33:1151-1157
- III. **Höifödt Lidö H**, Ericson M, Marston H, Söderpalm B. A Role for Accumbal Glycine Receptors in Modulation of Dopamine Release by the Glycine Transporter-1 Inhibitor Org25935. *Under revision, Frontiers in Psychopharmacology, Jan 2011*
- IV. **Höifödt Lidö H**, Marston H, Ericson M, Söderpalm B. The Glycine Reuptake Inhibitor Org24598 and Acamprosate Reduce Ethanol Intake in the Rat; Tolerance Development to Acamprosate but not to Org24598. *Under revision, Addiction Biology, Jan 2011*



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Abstract

Alcohol addiction and abuse is a main contributor to the global burden of disease and is a high public health priority. Alcohol addiction is a chronically relapsing neurobiological disorder affecting multiple neurotransmitter systems. Considerable evidence suggests that the mesolimbic dopamine system is the primary substrate for the acute rewarding and reinforcing effects of alcohol. Over time, excessive alcohol intake causes chronic functional changes in this system that may trigger off the transition from controlled recreational alcohol use to the compulsive intake that characterizes true addiction. Pharmacotherapy is emerging as a valuable tool for treatment of alcohol addiction, yet the current agents approved for this condition are only modestly effective and there is a need for improved treatments. It was recently revealed that extracellular glycine levels are important for regulating alcohol consumption and that the glycine receptor (GlyR) in nucleus accumbens (nAc) is an access point for alcohol to the mesolimbic dopamine system. The glycine transporter-1 protein (GlyT-1) is the main regulator of extracellular glycine concentrations and thus a key substrate for pharmacological manipulation of brain glycine levels. The aim of this thesis was to investigate (1) how modulation of extracellular glycine levels by inhibition of GlyT-1 affects the mesolimbic dopamine system, (2) how it interacts with alcohol-induced activation of mesolimbic dopamine, and (3) how GlyT-1 inhibition influences voluntary ethanol consumption. Effects on ethanol drinking were studied by using a limited access free-choice model in out-bred Wistar rats. Effects on dopamine and glycine levels in nAc were examined by using *in vivo* brain microdialysis. First it was demonstrated that the GlyT-1 blocker Org25935 robustly and dose-dependently reduced voluntary ethanol intake and that the effect was reinstated after an alcohol withdrawal period. Next it was shown that Org25935 raised extracellular glycine levels by 87% in nAc, increased dopamine levels *per se* and most importantly prevented an ethanol-induced dopamine increase in nAc. It was then shown that the GlyR in nAc rather than the NMDA receptor is involved in mediating the effect of Org25935 on dopamine levels in nAc. The last study investigated the anti-alcohol drinking profile of another selective GlyT-1 inhibitor Org24598, and compared the effect to that of acamprosate. In summary, the results propose that the GlyT-1 blocker Org25935 increases and stabilizes extracellular glycine levels which, via the GlyR, elevate and preserve a steady dopamine level, which in turn prevents additional ethanol-mediated GlyR activation and dopamine elevation. This adds to the growing evidence for the GlyR as an important player in the dopamine reward circuitry and in ethanol's effects within this system. Two different GlyT-1 inhibitors demonstrated an excellent ability to decrease ethanol consumption in experimental animals. This thesis proposes that GlyT-1 inhibition may represent a new concept for treatment of alcohol addiction.

Keywords: alcohol, dependence, dopamine, GlyT-1 inhibition, nucleus accumbens, reward

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